Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) for COVID-19

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Table of Contents

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BID	twice daily
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CYP3A	Cytochrome P4503A
DCC	Data Coordinating Center
DSMB	Data safety monitoring board
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report forms
EKG	Electrocardiogram
EUA	Emergency Use Authorization
FDA	Food & Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration
ICU	Intensive care unit
ID	Identification
IL1	Interleukin-1
IL6	Interleukin-6
IP	Investigational product
IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
IVY Network	Influenza Vaccine Effectiveness in the Critically Ill Network
KDIGO	Kidney Disease Improving Global Outcomes
LFT	Liver function test
LPV/r	Lopinavir/ritonavir
MERS-CoV	Middle East respiratory syndrome coronavirus 2
NHLBI	National Heart, Lung, and Blood Institute

NIH	National Institutes of Health
PI	Principal investigator (a clinician responsible for one site)
PK/PD	Pharmacokinetics/pharmacodynamics
PPE	Personal protective equipment
QD	once daily
QR code	Quick response code
QTc	QT interval corrected for heart rate
REDCap	Research Electronic Data Capture
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sIRB	Single IRB
SUSAR	Suspected unexpected serious adverse reaction
US	United States
VCC	Vanderbilt Coordinating Center
VAS	Visual Analog Scale

1. STUDY SUMMARY

Title	Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window
Acronym	TREAT NOW
Background	Effective therapies for COVID-19 are urgently needed. **Lopinavir/Ritonavir** (Kaletra) is an antiviral agent used to treat HIV-1 and is a potent *in vitro* inhibitor of SARS-CoV-2, the virus that causes COVID-19. Initial clinical data have suggested possible relevance as a potential therapeutic agent early in the course of patients with COVID-19.
Study Design	Blinded, multicenter, placebo-controlled randomized clinical trial
Intervention Group	Lopinavir/ritonavir 400 mg/100 mg orally twice daily for twenty-eight doses (Days 1-14)
Control Group	Placebo (unmatched) orally twice daily for 14 days
Sample Size	Up to 600 patients
Inclusion Criteria	1. Age ≥18 years 2. Laboratory-confirmed SARS-CoV-2 infection by RT-PCR or other molecular test, or by antigen test with emergency use authorization or full approval and collected within the past 6 days 3. Current symptoms of acute respiratory infection for ≤6 days, defined as one or more of the following: o cough o fever o shortness of breath o chest pain o abdominal pain o nausea/vomiting o diarrhea o body aches o weakness/fatigue
Exclusion Criteria	1. Prisoner 2. Pregnancy 3. Breast feeding 4. Two individuals from the same household are not enrolled in the study 5. Unable to randomize within 6 days after onset of acute respiratory infection symptoms 6. Hospitalization within the 6 days prior to randomization 7. Inability to swallow oral medications 8. Refusal or inability to be contacted and participate in daily symptom/safety monitoring in English or Spanish during the two-week follow-up period 9. Previous enrollment in this trial 10. Known severe chronic kidney disease requiring dialysis

	11. Known liver disease (cirrhosis or >3 times upper limit of normal for AST or ALT in medical record if available) 12. Known hepatitis B or hepatitis C infection 13. Known history of jaundice 14. Current heavy alcohol use, defined as 8 drinks or more per week for women or 15 drinks or more per week for men 15. Known seizure disorder 16. Known HIV infection 17. Known history of pancreatitis 18. Known history of prolonged QT interval (Long QT Syndrome, patient report, or QTc >500 milliseconds on most recently available electrocardiogram within the past 2 years) 19. Receipt of >1 dose of lopinavir/ritonavir in the 10 days prior to enrollment 20. Known allergy to lopinavir/ritonavir 21. Currently prescribed (with planned continuation) or planned administration during 14-day study period of medication at high risk for QT prolongation as follows: *Antiarrhythmics:* Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, procainamide, propafenone, quinidine, sotalol *Anti-cancer:* Arsenic trioxide, oxaliplatin, vandetanib *Antidepressants:* Amitriptyline, citalopram, escitalopram, imipramine *Antimicrobials:* azithromycin, ciprofloxacin, clarithromycin, erythromycin, fluconazole, levofloxacin, moxifloxacin, pentamidine, hydroxychloroquine *Antipsychotics:* aloperidol, chlorpromazine, droperidol, olanzapine, pimozide, quetiapine, thioridazine, risperidone, ziprasidone *Others:* cilostazol, cimetidine, cisapride, donepezil, methadone, ondansetron, sumatriptan 22. Currently prescribed (with planned continuation) or planned administration during 14-day study period of any of the following medications: alfuzosin, apalutamide, astemizole, ergot-containing medicines (including dihydroergotamine mesylate, ergotamine tartrate, methylergonovine), lomitapide, lovastatin, lurasidone, midazolam, phenobarbital, phenytoin, ranolazine, rifampin, sildenafil, simvastatin, rivaroxaban, St. John's Wort, terfenadine, triazolam. Patients who are on warfarin or fluticasone will be advised to contact their primary care provider to advise them that they are in the trial and possibly receiving lopinavir/ritonavir which can influence levels of either drug and may require more frequent monitoring.
Randomization	Eligible patients will be randomized through a central electronic system in a 1:1 ratio, to lopinavir/ritonavir (intervention) versus placebo (control). Randomization will be stratified by site and age (≥65 years or <65 years).
Blinding	Patients, treating clinicians, trial personnel, and outcome assessors will be blinded to group assignment.
Primary Outcome	Modified COVID Ordinal Outcomes Scale to Study Day 15: 1. Death

	2. Hospitalized on mechanical ventilation or ECMO 3. Hospitalized on supplemental oxygen 4. Hospitalized not on supplemental oxygen 5. Not hospitalized with symptoms and limitation in activity 6. Not hospitalized with symptoms but with no limitation in activity 7. Not hospitalized without symptoms nor limitation in activity
Secondary Outcomes	• Modified COVID Ordinal Outcome Scale to Study Day 8 • Modified COVID Ordinal Outcome Scale to Study Day 29 • Proportion of patients hospitalized to Study Day 29 • Time to hospitalization to Study Day 29 • Time to symptom resolution to Study Day 29 • All-cause, all-location mortality to Study Day 29 • Oxygen-free days through Study Day 29 • Fever-free days to Study Day 29 • Ventilator-free days through Study Day 29 • Vasopressor-free days through Study Day 29 • ICU-free days through Study Day 29 • Hospital-free days through Study Day 29
Safety Outcomes	• Seizure • Atrial or ventricular arrhythmia • Cardiac arrest • *Elevation in aspartate aminotransferase or alanine aminotransferase to twice the local upper limit of normal AND at least doubling over known baseline • *Acute pancreatitis • *Acute kidney injury by KDIGO criteria • Receipt of renal replacement therapy • *Symptomatic hypoglycemia • *Anemia or thrombocytopenia • Severe dermatologic reaction *For participants whose symptoms are significant enough to trigger a clinical work-up and thus have clinically available testing
Analysis	Using intention-to-treat principles, we will compare the primary outcome (Modified COVID Ordinal Outcomes Scale score on Study Day 15) between patients the intervention group (lopinavir/ritonavir) and the control group using a proportional odds model, adjusted for the following co-variables: age, gender, and duration of acute respiratory infection symptoms prior to randomization. With type I error of 0.05, enrolling 540 patients in the primary population will provide 90% power to detect an odds ratio of 1.75. Accounting for a 10% loss to follow-up rate, we will plan to enroll **600 patients**. This sample size and power assumes a frequentist analysis, which is generally more conservative than what is needed for a Bayesian approach. We will plan an initial DSMB evaluation for

	safety and feasibility after n=100 patients have been enrolled; efficacy will not be considered at this analysis. The trial will then have frequent interim analyses with details on specifics on timing of meetings, as well as efficacy and futility stopping rules to be detailed in the Statistical Analysis Plan, to be finalized prior to the n=100 interim analyses.

2. TRIAL DESCRIPTION

2.1 Background

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious illness caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2).[1,2] Although the epidemiology is not fully elucidated, most adults with COVID-19 appear to experience fever, cough, and fatigue and then recover within 1-3 weeks. However, a portion of adults with COVID-19 develop severe illness, typically manifesting as pneumonia and hypoxemic respiratory failure, with continued progression to acute respiratory distress syndrome (ARDS) and death in some cases.[1–3] There is an urgent need for outpatient therapies with a demonstrated ability to improve recovery progression of COVID-19 to severe illness. Based on mechanism of action and early clinical experiences, several agents currently available in the U.S. are proposed as potential therapies to prevent disease progression.[4–6] Among these potential therapies, lopinavir/ritonavir has generated substantial interest due to antiviral and immunomodulatory activity and established safety profiles with FDA approval for use in other conditions. In this trial, we will evaluate effectiveness and safety of lopinavir/ritonavir for the early treatment of adults with COVID-19 in the outpatient setting, prior to hospitalization.

2.1.1 COVID-19 Infection

COVID-19 was first identified as a cluster of cases of pneumonia among a group of workers from a seafood wholesale market in Wuhan, China in November 2019.[7] This observation, along with subsequent viral genotyping showing significant genetic similarities to the bat coronaviruses[8] suggest a zoonotic origin, although the specific reservoir and intermediary species remain unclear.[9] The COVID-19 infection represents the seventh coronavirus known to cause disease in humans.[10] Four of the coronaviruses viruses are known to cause symptoms of the common cold in immunocompetent individuals while two others (SARS-CoV and MERS-CoV) have caused recent outbreaks of severe and sometimes fatal respiratory diseases.[11] SARS-CoV-2 appears to exploit the same cellular receptor as SARS-CoV and MERS-CoV,[12] and its severity may similarly result from a predilection for intrapulmonary epithelial cells over cells of the upper airways.[13,14]

Since the first documented human case, COVID-19 has spread exponentially with 1,447,412 confirmed cases and 93,425 deaths worldwide as of April 9, 2020. While most patients recover after a mild, brief illness with fever and cough, the disease has a clinical spectrum ranging from asymptomatic infection[15] to ARDS and death.[16] The most common reasons for ICU care are respiratory failure and ARDS, with a minority developing shock and possibly cardiomyopathy.[17] The case fatality rate is estimated to be 0.25% to 3.0%.[18]

2.1.2 Promising Candidate Therapies for COVD-19

Several agents currently available in the US are proposed as potential therapies to halt disease progression.[4-6]

Lopinavir/ritonavir (Kaletra), an antiretroviral medication used to treat HIV-1, also has potent antiviral activity and promising early clinical data against coronaviruses, including those causing SARS and MERS.[22–26] Lopinavir is a HIV type 1 aspartate protease inhibitor; when combined with ritonavir, the plasma half-life of lopinavir is increased. Lopinavir was first identified as a potential therapy for severe

coronaviruses as demonstrating strong *in vitro* inhibitory activity against both SARS-CoV, the virus which causes Severe Acute Respiratory Syndrome (SARS), and MERS-CoV, the virus which causes Middle East Respiratory Syndrome (MERS).[27,28] Prior open label studies of lopinavir-ritonavir suggested the potential to improve clinical outcomes and decrease viral load in patients with SARS and MERS.[29–32]

A recent randomized open-label trial of lopinavir/ritonavir in hospitalized patients with COVID-19 failed to demonstrate a treatment benefit.[3] However, the trial was underpowered for clinically important endpoints and enrolled patients at an advanced stage of disease, a median of 13 days after symptom onset, when antiviral activity is likely much less important. Still, the observed mortality in the lopinavir/ritonavir group was 5.8% lower than the control group (95% confidence interval, -17.3 to 5.7), as well as an observed faster time to clinical improvement that was also not statistically significant (HR 1.24, 95%CI 0.90-1.72). Accordingly, substantial enthusiasm remains for early treatment of COVID-19, particularly prior to hospitalization.

2.1.3 Rationale for a Randomized Trial Early Treatment among Outpatients

Initial COVID-19 symptoms develop approximately 2-10 days after infection with the SARS-CoV-2 virus.[33–35] Most adults recover without complications, but hospitalized patients typically experience pneumonia leading to acute hypoxemic respiratory compromise/failure, and in some cases, ARDS and death. The first 4-8 days of illness typically manifest with conditions consistent with a viral syndrome such as fevers and cough. Those experiencing a milder course typically recover after this initial period; those on a more severe course will progress to respiratory failure and ARDS, which usually occurs 7-12 days after the onset of symptoms.[36,37]

The period between onset of symptoms and the development of hypoxemia requiring hospitalization is a critical therapeutic window for treatment to halt disease progression. Early data suggest that mortality rates are highest in the elderly, immunocompromised, and those with chronic cardiopulmonary disease. However, young adults remain at high risk of complications, as younger adults (age 20-44 years) comprise approximately 25% of COVID-19-hospitalized patients.

COVID-19 is an unprecedented public health crisis, and there is significant interest in finding effective therapies, specifically in repurposing approved medications with widespread availability and known safety profiles. Efficacy and safety data for lopinavir/ritonavir from randomized trials are critical to provide evidence-based therapy for the ongoing COVID-19 pandemic. Our proposed trial will efficiently assess the potential candidate therapy and provide a structure for rapid integration of other candidate drugs in future clinical trials.

2.2 Study Aims

2.2.1 Study aim

To determine the effectiveness and safety of early treatment with lopinavir/ritonavir versus placebo in outpatient adults with COVID-19.

2.2.2 Study hypothesis

Early initiation of lopinavir/ritonavir will reduce disease progression and improve clinical outcomes among outpatient adults with COVID-19.

2.3 Study Design

We will conduct an investigator-initiated, multicenter, blinded, placebo-controlled, randomized clinical trial evaluating lopinavir/ritonavir vs placebo for early treatment of adults with COVID-19 in the outpatient setting prior to hospitalization. Patients, treating clinicians, and study personnel will all be blinded to study group assignment.

3. STUDY POPULATION AND ENROLLMENT

3.1 Inclusion Criteria

1. Age ≥18 years
2. Laboratory-confirmed SARS-CoV-2 by RT-PCR or other molecular test, or by antigen test with FDA emergency use authorization or full approval and collected within the past 6 days
3. Current symptoms of acute respiratory infection for ≤6 days, defined as one or more of the following:
    - cough
    - fever
    - shortness of breath
    - chest pain
    - abdominal pain
    - nausea/vomiting
    - diarrhea
    - body aches
    - weakness/fatigue

3.2 Exclusion Criteria

1. Prisoner
2. Pregnancy
3. Breast feeding
4. Two individuals from the same household are not enrolled in the study
5. Unable to randomize within 6 days after onset of acute respiratory infection symptoms
6. Hospitalization within the 6 days prior to randomization
7. Inability to swallow oral medications
8. Refusal or inability to be contacted and participate in daily symptom/safety monitoring in English or Spanish during the two-week follow-up period
9. Previous enrollment in this trial
10. Known severe chronic kidney disease requiring dialysis
11. Known liver disease (cirrhosis or >3 times upper limit of normal for AST or ALT in medical record if available)
12. Known hepatitis B or hepatitis C infection
13. Known history of jaundice
14. Current heavy alcohol use, defined as 8 drinks or more per week for women or 15 drinks or more per week for men
15. Known seizure disorder

16. Known HIV infection
17. Known history of pancreatitis
18. Known history of prolonged QT interval (Long QT Syndrome, patient report, or QTc >500 milliseconds on most recently available electrocardiogram within the past 2 years)
19. Receipt of >1 dose of hydroxychloroquine, chloroquine, or lopinavir/ritonavir in the 10 days prior to enrollment
20. Known allergy to lopinavir/ritonavir
21. Currently prescribed (with planned continuation) or planned administration during 14-day study period of medication at high risk for QT prolongation as follows:
    Antiarrhythmics: Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, procainamide, propafenone, quinidine, sotalol
    Anti-cancer: Arsenic trioxide, oxaliplatin, vandetanib
    Antidepressants: Amitriptyline, citalopram, escitalopram, imipramine
    Antimicrobials: azithromycin, ciprofloxacin, clarithromycin, erythromycin, fluconazole, levofloxacin, moxifloxacin, pentamidine, hydroxychloroquine
    Antipsychotics: aloperidol, chlorpromazine, droperidol, olanzapine, pimozide, quetiapine, thioridazine, risperidone, ziprasidone
    Others: cilostazol, cimetidine, cisapride, donepezil, methadone, ondansetron, sumatriptan
22. Currently prescribed (with planned continuation) or planned administration during 14-day study period of any of the following medications: alfuzosin, apalutamide, astemizole, ergot-containing medicines (including dihydroergotamine mesylate, ergotamine tartrate, methylergonovine), lomitapide, lovastatin, lurasidone, midazolam, phenobarbital, phenytoin, ranolazine, rifampin, sildenafil, simvastatin, rivaroxaban, St. John's Wort, terfenadine, triazolam. Patients who are on warfarin or fluticasone will be advised to contact their primary care provider to advise them that they are in the trial and possibly receiving lopinavir/ritonavir which can influence levels of either drug and may require more frequent monitoring.

3.3 Justification of Exclusion Criteria

Since this is intended as an outpatient trial, patients hospitalized within 6 days prior to enrollment/randomization are excluded. The other exclusion criteria are primarily designed for patient safety. In addition to excluding specific vulnerable populations (e.g., prisoners), these criteria are designed to exclude patients for whom receipt of lopinavir/ritonavir might increase the risk of serious adverse events. Lopinavir/Ritonavir has been routinely prescribed to outpatients with HIV-1 without extensive cardiac workups, laboratory testing, or monitoring. In addition, we have incorporated guidelines for safe outpatient prescribing of lopinavir/ritonavir without a baseline electrocardiogram or outpatient cardiac monitoring[40] and have put into place a method of monitoring newly prescribed medications during the 14-day intervention period.

3.4 Screening

The site investigator or delegate will screen for non-hospitalized patients with laboratory confirmed COVID-19 (that is, a positive laboratory test for SARS-CoV-2 by RT-PCR or other molecular method, or by antigen test with FDA approval or emergency use authorization and collected within the past 6 days). The source of these patients will be primarily patients seen and sent home from the enrolling hospital

emergency department, urgent care, primary care, virtual care/telemedicine visits, or testing centers. We may also advertise the study at outpatient testing sites and more broadly for self-referral to the study.

3.5 Assessment of Eligibility and Exclusion Tracking

For patients who appear to meet eligibility criteria after screening, we will complete an electronic case report form to determine eligibility and track exclusions. We will access and store the electronic case report form in the electronic database. At the time of entry into the screening database, we will assign the patient a screening number.

If a patient appears to meet all eligibility criteria, the site investigator or delegate will approach the patient to confirm eligibility, discuss potential study recruitment, and proceed with informed consent. Most patients will no longer be in the healthcare setting and therefore we anticipate that this discussion will occur primarily by telephone or videophone to the patient's home (test pending patients are typically advised by their clinicians to home quarantine while symptomatic and test results are pending). We may advertise the study at both the testing sites as well as more broadly.

For all excluded patients, including refusal by the patient to participate, we will collect a small number of variables, including month and year patient met screening criteria and reason(s) patient was excluded to allow for reporting in the CONSORT diagram of the manuscript. Due to the nature of this trial in the outpatient setting and for staff safety and personal protective equipment (PPE) conservation, these encounters will usually occur via telephone or videophone.

3.6 Process of Obtaining Informed Consent

We will obtain written informed consent from the patient. We will not enroll patients who lack decision-making capacity due to logistical issues with remote study medication administration, safety monitoring, and accurate data collection.

In-person visits for patients with known COVID-19 who are deemed stable for outpatient management and home quarantine would violate infection control principles and policies. Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), there is a moral and practical imperative to minimize face-to-face contact between patients and non-clinical personnel. Therefore, we will use "no-touch" consent procedures for this trial, employing an electronic remote consent process to obtain written informed consent.

Electronic approach

1. A link for the electronic consent is sent to the subject.
2. Research staff contact the patient by telephone or videophone (method dictated by institutional policy) to have an informed consent conversation. *This step confirms subject identity*.
3. If they consent, the patient signs the consent form. This can be:
    a. an actual signature (often tracing their finger on the screen) OR
    b. a username and password specific to the individual signing

This approach complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), https://www.hhs.gov/ohrp/regulations-and-

policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

We will provide the information for the informed consent discussion in a formal document that has been approved by the IRB and in a language comprehensible to the potential participant, using an interpreter if necessary. Currently, English and Spanish documents are approved for use in this trial. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks or benefits of taking part. We will clearly state that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Where a patient does not speak English, a translated Spanish consent and qualified interpreter will be employed, using similar "no-touch" principles. Use of a telephone or video interpreter and the interpreter's identity will be documented on the electronic consent.

After allowing the potential participant time to read the informed consent document, research staff will answer any additional questions.

3.7 Randomization and Blinding

We will randomize eligible participants through a central electronic system in a 1:1 ratio to lopinavir/ritonavir (intervention) versus placebo (control). A randomized group assignment is provided to the site investigator or delegate from a centralized, web-based platform. Randomization will require provision of the screening number and confirmation of patient eligibility. In the future, we may also consider adding an intervention group.

We will perform the randomization in permuted blocks of varying size and stratified by site and age (≥65 years or <65 years). We will store the randomization sequence allocation on a secure server, which will not be available to site study personnel. Each participant will receive a computer-generated study ID number. The computer-generated study ID number and shipping information will be provided to the pharmacy who will provide a dose pack containing lopinavir/ritonavir or placebo.

The participant, treating clinicians, study personnel, and outcome assessors will all remain blinded to group assignment until after the database is locked and blinded analysis is completed. Only Belmar Pharmacy, who is distributing study medication, and one member of the biostatistical team who is preparing closed DSMB interim reports will be unblinded. Specifically, study medication will be dispensed with packaging and labelling that would blind treatment assignment. Unblinding will occur only if required for subject safety or treatment at the request of the treating clinician.

4. STUDY INTERVENTIONS

4.1 Treatment of Study Participants

A summary of the trial's schedule of events is included in Appendix A.

Timing of study procedures is based on the time of randomization, which is defined as "Time 0". Study Day 1 is defined as the day of receipt of the first dose of study drug. We will assess the primary outcome on Study Day 15, which corresponds to 14 days (2 weeks) after the initiation of study drug.

A research physician will prescribe a study medication that a central pharmacy (Belmar Pharmacy) will fill at no charge to the patient and will arrive through overnight mail (typically next day by 10:00AM). The study medication will arrive in blinded blister packs labelled as lopinavir/ritonavir or placebo with the appropriate daily instruction for administration. The goal is initiation of treatment within one day of randomization (Study Day 1).

On Study Days 1-15, the patient will complete brief electronic data collection form through a secure electronic platform that will confirm receipt and administration of study drug and document the number and reason for any missed doses. For those with missing electronic data, telephone follow-up will provide an additional opportunity to clarify study drug administration, as needed. If the participant is hospitalized prior to completion of the study medication, an attempt will be made to continue study medication. However, study medication may be discontinued if felt necessary by the treating clinician in consultation with the local investigator. Unblinding will occur only if required for subject safety or treatment at the request of the treating clinician.

4.2 Lopinavir/Ritonavir Group

Participants assigned to the lopinavir/ritonavir arm will receive lopinavir/ritonavir 400 mg/100 mg orally twice daily for 28 doses (Days 1-14). Medication dose packs will contain all 28 doses labelled by Study Day.

Rationale for Drug Selection of Lopinavir/Ritonavir

We are administering lopinavir/ritonavir (LPR/r) in standard dosing: lopinavir/ritonavir 400 mg/100 mg twice daily for 28 doses (Days 1-14). LPV/r as Kaletra tablets is dosed based upon extensive PK/PD study evaluations in healthy and HIV+ subjects as reported in its US and European labels (400/100mg BID or 800/200mg QD) - see https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021251s052_021906s046lbl.pdf and https://www.medicines.org.uk/emc/product/221/smpc. The mean in vitro antiviral IC_{50} of lopinavir against HIV in the absence of human serum, is 6.5 nM. The IC_{50} of LPV vs SARS viruses and in particular SARS-CoV-2 is believed to be approximately 1-10µM.[23,25] Comparison of these potencies is limited as data are uncontrolled and assay procedure differ, but it suggests SARS-CoV-2 replication is approximately 100 - 1000-fold less susceptible to LPV/r-mediated replication than HIV. PK/PD comparisons across unrelated viral infections with overtly different clinical manifestations also presents significant translational insight limitations, but the safety/efficacy and PK/PD for LPV/r against HIV is well known and enables a guide to a pragmatic and safety-reasoned dosing regimen. A regimen of 400/100 mg BID should achieve near steady state concentrations as seen in HIV therapy within 3 to 4 days. This should align with an acceptable safety profile coupled with rapid achievement of LPV/r exposure to efficacious levels associated with HIV clinical antiviral activity, and possibly some effect on SARS-C0V-2 replication inhibition in patients. LPV/r dosing BID, or 800/200mg QD in adults enables unbound LPV exposure at significantly higher levels than reported by the HIV in vitro antiviral IC_{50}. Multiple dosing with 400/100 mg LPV/r twice daily for 14 days produces mean ± SD LPV peak plasma concentration (Cmax) of 12.3 ± 5.4 µg/ml. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/ml. LPV AUC over a 12 hour dosing interval averages 113.2 ± 60.5 µg/h/m. LPV and RTV are 98–99% bound to the blood plasma proteins, which indicates that unbound LPV exposure to be approximately 10 - 100-fold greater than the in vitro HIV IC_{50} value, and within an

order of magnitude as reported for SARS-C0V-2 value, thereby making clinical testing by the regimen described as reasoned-from a potential antiviral perspective. If unbound drug levels are higher inpatient BAL fluid, then a more favourable ratio is potentially achievable.

4.3 Control Group

Participants randomized to the control group will receive placebo orally twice daily for 14 days. Medication dose packs will contain all 28 doses labelled by Study Day.

While patients who receive the lopinavir/ritonavir will not have a matched placebo, the packaging would indicate study medication (lopinavir/ritonavir, or placebo) and participants will not be aware that there is no matched placebo for lopinavir/ritonavir. Thus, even if the participant searches the internet for pill markings, it is entirely possible from the patient perspective that this could be a marched placebo. Exclusion criteria will be exercised to ensure that two individuals from the same household are not enrolled in the study and that telephone assessments during the study avoid discussion of the appearance of the study medication.

4.4 Co-Interventions

This trial will control the use of lopinavir/ritonavir, or placebo during the 14-day intervention period. Enrolled participants will not receive open-label lopinavir/ritonavir during the 14-day intervention period, unless the patient is hospitalized, and the treating clinician wishes to unblind the trial and use these medications open label. The treating clinicians will make all other treatment decisions without influence from the protocol. Administration of other antiviral, immunomodulatory, or other COVID-19 directed novel medications ("rescue therapy") will be allowed. We will record the co-administered COVID-19 directed medications in the case report form. The patient will be allowed to take antipyretics at home as needed.

4.5 On-Study Monitoring

All participants enrolled in the study will be outpatients (not hospitalized) and therefore initial monitoring will be remote as part of routine outpatient clinical care with treating physicians and nurses (we anticipate primarily virtual care/telehealth or routine telephone follow-up). The research staff will provide additional remote monitoring through daily electronic collection of symptoms, healthcare utilization, clinically obtained electrocardiograms, newly prescribed medications, and adverse event reporting with supplemental telephone follow-up as needed. The research team may flag potential issues but will defer specific decisions about additional care and hospital transfer to usual outpatient clinical care. Lopinavir/ritonavir has been used extensively for outpatient treatment of other conditions without the need for additional monitoring during short term therapy.

Between baseline and Study Day 15, study personnel will ascertain and review the initiation of any new medications daily and evaluate for potential medication interactions with lopinavir/ritonavir (see Appendix B). If a medication that is considered to be contraindicated with lopinavir/ritonavir is discovered, site physician investigator or designee will contact the patient to discuss if stopping study drug is appropriate or if the medication in question may be stopped or substituted in consultation with the prescribing/treating clinician. If a medication with a potential interaction with lopinavir/ritonavir is identified, study personnel will contact the treating clinician to ensure they are aware of the potential interaction, as needed. Treating clinicians will determine whether an alternative medication would be

appropriate or whether the risk-benefit ratio favors continuing the medication with the known potential interaction.

4.6 Criteria for Stopping Study Drug

We will stop administration of the blinded study drug temporarily or permanently for (a) adverse events without evidence of an alternative cause to the patient's symptoms, (b) results of on-study monitoring, or (c) clinical deterioration if requested by treating clinician.

If a patient experiences an adverse event that the patient treating clinicians, or investigators feel merits temporarily or permanently stopping the study drug, we will stop the study drug. We will record the explanation for stopping the study drug in the case report form, and we will record and report the adverse event according to the adverse event guidelines below. If the adverse event resolves to the extent that the patient, treating clinicians, and investigators feel that resuming the study drug is appropriate, we will resume the study drug, and we will record this information in the case report form.

If an EKG is obtained as part of routine clinical care after enrollment and the QTc is greater than or equal to 500 ms, we will discontinue the study drug, unless a repeat EKG after at least 24 hours demonstrates the QTc is less than 500 ms, at which time we will direct the patient to resume the study drug. We will record both the value for the QTc and the decision to continue or stop the study drug in the case report form. If the daily on-study monitoring by study personnel for medication interactions indicates a potential interaction with a medication that treating clinicians feel is required for the optimal treatment of the patient and with which treating clinicians and the investigator feel it would be unsafe to administer lopinavir/ritonavir, we will stop study drug and record the reason in the case report form.

For patients who experience clinical deterioration requiring hospitalization or toxicity potentially related to study drug, for which treating clinicians feel optimal care would include stopping the study drug and unblinding group assignment, we will stop the study drug, and the site investigator will contact the coordinating center to receive the unblinded study group assignment. We will defer any additional treatments to the treating clinicians. In this situation, we will record the following data in the case report form: the criteria met for clinical deterioration; the reason for stopping study drug and unblinding; use of other antivirals, and immunomodulators; and study outcomes. Crossovers from placebo to lopinavir/ritonavir will be recorded and reported to the DSMB at DSMB reviews and interim analyses. The primary analysis will be intention-to-treat.

5. OUTCOMES

5.1 Primary Outcome

The **primary outcome** is clinical status on the Modified COVID Ordinal Outcomes Scale to Day 15, incorporating more granular description of symptoms at the milder end of the scale for this outpatient trial. In addition, we collapsed non-invasive ventilation with mechanical ventilation and high flow nasal oxygen with supplemental oxygen to improve pragmatism of in-hospital data collection (source data may come from the patient or alternate contact if hospital records are not accessible). This outcome is in use by COVID-19 trials globally, including those conducted by the World Health Organization, and will facilitate pooling and comparison of data across trials.

1. Death

2. Hospitalized on mechanical ventilation or ECMO
3. Hospitalized on supplemental oxygen
4. Hospitalized not on supplemental oxygen
5. Not hospitalized with symptoms and limitation in activity
6. Not hospitalized with symptoms but with no limitation in activity
7. Not hospitalized without symptoms or limitation in activity

5.2 Secondary Outcomes

- Modified COVID Ordinal Outcome Scale at Study Day 8
- Modified COVID Ordinal Outcome Scale at Study Day 29
- Proportion of patients hospitalized to Study Day 29
- Time to hospitalization to Study Day 29
- Time to symptom resolution to Study Day 29
- All-cause, all-location mortality to Study Day 29
- Oxygen-free days through Study Day 29
- Fever-free days to Study Day 29
- Ventilator-free days through Study Day 29
- Vasopressor-free days through Study Day 29
- ICU-free days through Study Day 29
- Hospital-free days through Study Day 29

5.3 Safety outcomes

- Seizure
- Atrial or ventricular arrhythmia
- Cardiac arrest
- *Elevation in aspartate aminotransferase or alanine aminotransferase to twice the local upper limit of normal, AND at least doubling over known baseline
- *Acute pancreatitis
- *Acute kidney injury by KDIGO criteria
- Receipt of renal replacement therapy
- *Symptomatic hypoglycemia
- *Anemia or thrombocytopenia
- *Severe dermatologic reaction

*For participants whose symptoms are significant enough to trigger a clinical work-up and thus have clinically available testing and diagnoses:

5.4 Rationale for Primary Outcome

COVID-19 has a broad spectrum of clinical severity. Among non-hospitalized patients, most recover without experiencing critical illness.[42] Designing a trial with statistical power to detect a meaningful difference in hospital-free days, ICU-free days, or mortality might require an unfeasibly large sample size and could miss significant morbidity experienced by outpatients with COVID-19. Since the majority of

morbidity from COVID-19 relates to hypoxemia, the fact that this outcome is tied to degree of hypoxemic respiratory failure increases its face validity and relevance. For similar reasons, previous trials of severe influenza have employed a similar ordinal outcome.[43] This ordinal scale was selected as an outcome in multiple ongoing COVID-19 trials across a range of illness severity, including outpatients, and is a preferred outcome by the World Health Organization Research and Development Blueprint for COVID-19.[44] For our cohort of outpatients, we have enhanced the outcome with the addition of COVID-related symptoms to better distinguish recovery in those with milder disease. Use of this standardized outcome will increase the potential to compare the results of this trial with other trials and perform meta-analyses.

6. DATA COLLECTION

Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), we will have no face-to-face contact between patients and non-clinical staff. Additionally, minimizing research activities and conducting the trial in a pragmatic manner will increase the ability to complete the trial in the face of strained clinical and research resources during the COVID-19 pandemic. We will emphasize data collection by electronic methods, supplemented by telephone or videophone follow-up and from the electronic health record. If the patient is hospitalized, we will attempt to obtain permission for accessing these records. We will not collect biological specimens as part of this trial.

Electronic Data Collection:
We will collect data directly from patients using MyCap or, if installation and use of an app is not possible, through text messaging or email with a survey link, or phone call as back up. MyCap is a secure mobile application developed by the REDCap team at Vanderbilt and integrated into the REDCap database system. Participants install the application on their personal device. All interaction with the app is secure and requires the user to enter a 6-digit pin. Once a patient has consented, they join a study for data collection by scanning a unique QR code. Then, patients receive a notification each day to answer questions about their current symptom burden, any hospitalizations, and any oxygen requirements. This provides the capacity for collecting patient reported outcomes in a secure and robust manner. If patients are unable to use this application or unwilling to install it, they can be asked the same messages using a text messaging system will be utilized. Our outcomes are designed such that a text messaging option is not overly burdensome and can even be completed in hospitalized patients. The process for using text messaging is HIPAA compliant. Finally, we can use standard telephone calls as a back-up method to administer the questions. This minimizes loss to follow up and maximizes the efficiency of the study. Research teams have had great success using REDCap-based mobile data collection for multiple studies including collection of data about quality of life and exercise after heart surgery (NCT03270124), pain reporting in sickle cell disease (NCT03629678), and pain using a visual analog scale (VAS) during an interventional drug study (NCT03865940).

Telephone/Videophone Data Collection:
While primary data collection will be by electronic methods as above, specific circumstances will trigger telephone or videophone follow-up, based on the following:

- Participant does not complete daily electronic data collection for two consecutive days.
- Participant does not complete Study Day 29 assessment
- Identification of newly prescribed medication if deemed necessary by site investigator.
- New electrocardiogram

- Lack of administration of study medication, if unable to confirm plan to resume study medication
- Hospitalization
- Reported adverse events, if deemed necessary by the site investigator
- Clarification or concern by study team
- By request of participant

6.1 Baseline Variable Collection

- Informed Consent Document and documentation of consent process
- Presence or absence of each inclusion and exclusion criterion
- Date and time of enrollment
- Day of symptom onset
- Specimen type, date, and result of SARS-CoV-2 testing conducted clinically.
- Demographics (age, sex, race, ethnicity, height, weight)
- Comorbidities: chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, chronic neurological disease, malignant neoplasm, chronic hematologic disease, AIDS/HIV, obesity, diabetes with complications, diabetes without complications, rheumatologic disorder, malnutrition, smoking, other
- Chronic use of medication: ACE inhibitors, angiotensin receptor blockers
- Receipt of azithromycin in the past week
- Presenting signs and symptoms, along with self-reported severity

6.2 Daily Assessments between Randomization and Study Day 16, and then at Day 29

- Study drug administration and reason for missed doses.
- Modified COVID Ordinal Outcomes Scale
- Daily signs and symptoms, along with self-reported severity via electronic log and/or telephone interview.
- Day of symptom resolution
- Receipt of open label antivirals: chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, other
- Receipt of open label immunomodulators between enrollment and hospital discharge: corticosteroids, tocilizumab, sarilumab, interferon β, other
- Receipt of azithromycin
- Study days in hospital (if applicable)
- Study days receiving supplemental oxygen (if applicable)
- Study days receiving non-invasive or invasive mechanical ventilation (if applicable)
- Study days in ICU to Study Day 29
- Study day of death (if applicable)
- Safety Outcomes: seizure, atrial or ventricular arrhythmia, cardiomyopathy, cardiac arrest, aspartate aminotransferase or alanine aminotransferase levels that are greater than twice the local upper limit of normal (or two times higher than known baseline), acute pancreatitis (defined by a clinically obtained lipase level above the local upper limit of normal and abdominal pain or vomiting), stage II or greater acute kidney injury according to KDIGO criteria[45], receipt of new renal replacement

therapy, symptomatic hypoglycemia, neutropenia, lymphopenia, anemia, thrombocytopenia, or severe dermatologic reaction (e.g., Steven's Johnson Syndrome). Since we will not systematically obtain laboratory tests to identify asymptomatic changes in laboratory values, we will ask about outpatient laboratory testing or obtain the requisite results of laboratory tests from medical records if tests were obtained.

- Prolonged (>500 msec) QTc interval on available electrocardiograms
- Self-reported adverse events to Study Day 15

7. STATISTICAL CONSIDERATIONS

Using intention-to-treat principles, we will compare the primary outcome (Modified COVID Ordinal Outcomes Scale score to Day 15) between patients in each intervention group and the control group using a proportional odds model, adjusted for the following co-variables: age, gender, and duration of acute respiratory infection symptoms prior to randomization. The proportional odds assumption will mainly be examined using graphical methods—e. g., the logit of the empirical cumulative distribution function of the ordinal scale should be parallel among categories of covariates. If proportionality is clearly violated, we will consider partial proportional odds or non-proportional odds models.

With type I error of 0.05, enrolling 540 patients in the primary population will provide 90% power to detect an odds ratio of 1.75. Accounting for a ~10% loss to follow-up rate, we will plan to enroll **600 patients**. This sample size and power assumes a frequentist analysis, which is generally more conservative than what is needed for a Bayesian approach. We will plan an initial DSMB evaluation of safety and feasibility after n=100 patients have been enrolled; efficacy will not be considered at these analyses. The trial will then have frequent interim analyses with details on specifics on timing of meetings, as well as efficacy and futility stopping rules to be detailed in the Statistical Analysis Plan, to be finalized prior to the first interim analyses.

Additional analyses will include comparisons of secondary outcomes between treatment groups. We will compare the Modified COVID Ordinal Outcome Scale daily over the 14-day intervention period using a recently developed longitudinal proportional odds model that can incorporate the information on intermediate states between baseline and Study Day 15. For time-to-event outcomes we will utilize survival models (e.g., Cox proportional hazards models), continuous outcomes will utilize linear regression, and dichotomized outcomes will be evaluated using logistic regression. We will also evaluate primary and main secondary outcomes in key subgroups of interest. *A priori* subgroups for analysis will include age, sex, race/ethnicity, facility residence, BMI, baseline renal function, hypertension, diabetes, cardiovascular disease, and duration of respiratory symptoms.

The proposed trial will use a Bayesian approach to implement adaptive elements and to estimate the primary outcome using the proportional odds model to calculate the posterior probability that the OR > 1, suggesting any benefit. Additionally, we will calculate posterior probabilities to account for the potential that a treatment is ineffective (e.g., OR < 1) or causes harm (i.e., safety concerns) and would be of consideration to terminate enrollment due to futility. A Bayesian approach provides the ability for frequent updating of the posterior probabilities to rapidly identify if a treatment is showing benefit to reducing hospitalization and severity of disease, providing the possibility of more quickly identifying beneficial treatments. The proposed design may evolve as more is learned about COVID-19 and the

treatment responses, with an adaptive Bayesian design that we expect to be more efficient and flexible being in active development.

We expect that given the circumstances of this trial during a rapidly evolving pandemic, the DSMB will need maximum latitude in modifying this trial if necessary, based on other studies of lopinavir/ritonavir that may be conducted simultaneously and the rate of growth or decline of the epidemic. Alterations may include adding patients, adding arms to the trial, declining to stop for futility, or stopping earlier to make the results public if that is necessary. We may also need to collapse categories within the Modified COVID Ordinal Scale based on granularity of data or frequency of an individual category. We are exploring other possible statistical plans that will be included in a final statistical analysis plan and will be presented to the DSMB before the first interim report.

8. DATA QUALITY MONITORING AND STORAGE

8.1 Data Quality Monitoring

We will review data quality remotely using front-end range and logic checks at the time of data entry and back-end monitoring of data using application programming interface tools connecting the online database to statistical software to generate data reports.

8.2 Data Storage

Site personnel will enter study data into a secure online database. Site personnel will maintain the data in the secure online database until the time of study publication. At the time of publication, DCC will generate a de-identified version of the database.

9. RISK ASSESSMENT

9.1 Potential Risk to Participants

Although lopinavir/ritonavir are FDA approved medications with a long history of patient use and well-established safety profiles, potential risks exist to participating in this study of lopinavir/ritonavir versus placebo for the treatment of COVID-19.

9.1.2 Potential risks of receiving lopinavir/ritonavir

The safety and tolerability of lopinavir/ritonavir has been well characterized through clinical trials and post-marketing experience since first authorization for use in 2001 for the approved HIV indication with over 7 million patient years of exposure. Based on clinical trials and post-marketing experience, the most frequently reported adverse drug reactions among patients receiving lopinavir/ritonavir were gastrointestinal disorders (including diarrhea, nausea, vomiting, and upper and lower abdominal pain), fatigue/asthenia, respiratory tract infection (upper and lower), lipid elevations (hypercholesterolemia and hypertriglyceridemia), musculoskeletal pain (including arthralgia and back pain), and headache (including migraine). Key safety concerns include metabolic abnormalities such as dyslipidemia and insulin resistance, pancreatitis, and hepatotoxicity. In addition, in the HIV population, immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Grave's disease) has been reported.

Important potential risks include PR prolongation at therapeutic dosing, and QT prolongation with supratherapeutic doses. Lopinavir/ritonavir interacts with several drugs since it is an inhibitor of the P450 isoform CYP3A and is likely to increase the plasma concentration of drugs that are metabolized by CYP3A4. Therefore, LPV/r should not be co-administered with drugs primarily metabolized by CYP3A and for which elevated plasma concentrations are associated with serious and/or life-threatening events. A list of such products is included in the lopinavir/ritonavir label. Rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities, or in patients receiving drugs known to prolong the PR interval such as verapamil, have been reported in patients receiving lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients. In addition, QT prolongation with supratherapeutic doses and when lopinavir/ritonavir is co-administered with drugs known to prolong the QT interval has been reported. Because lopinavir/ritonavir is principally metabolized by the liver, caution should be exercised when administering this drug to patients with impaired hepatic function. Extra monitoring is recommended when diarrhea occurs. The relatively high frequency of diarrhea during treatment with lopinavir/ritonavir may compromise the absorption and efficacy (due to decreased compliance) of lopinavir/ritonavir or other concurrent drugs. Serious persistent vomiting and/or diarrhea with lopinavir/ritonavir use might also compromise renal function. The safety of lopinavir/ritonavir for treatment of patients with COVID-19 disease is unknown. COVID-19 may be associated with cardiac effects. lopinavir/ritonavir may prolong QT at supratherapeutic doses and prolong PR at therapeutic doses, resulting in arrhythmias.

9.1.3 Potential risks of receiving placebo with COVID-19

One potential risk to participating in this study is receiving placebo rather than lopinavir/ritonavir. This risk is only relevant if lopinavir/ritonavir are ultimately found to be an effective therapy for COVID-19 and is not relevant if lopinavir/ritonavir are both ultimately found to be ineffective therapy for COVID-19. This trial protocol minimizes this risk through rigorous design to minimize the number of patients that we must enroll to determine whether these therapies are an effective therapy for COVID-19 and allocating approximately one-third of eligible patients to placebo (instead of one half in a traditional two-arm trial). We will also exclude patients who decline to participate because they feel their optimal care requires lopinavir/ritonavir, exclude patients whose treating clinicians declines to allow enrollment because they feel the patient's optimal care requires treatment with lopinavir/ritonavir, and specify procedures for stopping the study drug, unblinding, and allowing open-label administration of lopinavir/ritonavir for patients who experience clinical deterioration during the study period.

9.2 Minimization of Risk

Federal regulations at 45 CFR 46.111(a)(1) require that risks to participants are minimized by using procedures which are consistent with sound research design. This trial protocol incorporates numerous design elements to minimize risk to patients that meet this human subject protection requirement. Lopinavir/ritonavir is approved by the U.S. Food and Drug Administration and have been used in clinical practice for decades in a number of patient populations with an established safety profile. The dose and route of administration of both medications in this trial are comparable to the dose and route of administration approved for the treatment of other acute infections, such as HIV-1. The duration of treatment in this trial of 14 days is significantly shorter than for treatment of HIV-1 infection, for which the drug is frequently administered for multiple years. To further mitigate risk, we will exclude patients

with specific risk factors for adverse events from study medication, we will exclude patients with higher risk for adverse events and patients receiving medications that may interact with lopinavir/ritonavir.

We will collect data on adverse events that are significant enough to warrant health care evaluation. It was determined that transient, and clinically insignificant changes in the electrocardiogram or laboratory testing would not be required. In addition, the additional risk to the public and to research personnel by exposing them to COVID-19 patients by requiring additional research testing is greater than the benefits of this monitoring. The trial protocol includes active monitoring of clinically significant adverse events, clinical outcomes, and interim analyses by an independent data and safety monitoring board empowered to stop or modify the trial at any time, including the need to request additional safety monitoring if determined to be warranted.

9.3 Potential Benefit

Study participants may or may not receive any direct benefits from their participation in this study. Administration of lopinavir/ritonavir may improve clinical outcomes among outpatient adults with COVID-19.

9.4 Risk in Relation to Anticipated Benefit

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits. Lopinavir/Ritonavir has been used in clinical practice for decades and previously evaluated for the treatment of patients acutely ill from infection with substantial data to support its safety and potential efficacy.

10. HUMAN SUBJECTS PROTECTIONS

Each study participant must sign and date an informed consent form or complete the consent in accordance with ethics committee guidelines for obtaining consent. Approval of the central institutional review board will be required before any participant is entered into the study.

10.1 Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. We will screen non-hospitalized patients with positive SARS-CoV-2 testing to determine if a patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine clinical care of the patient will be reviewed to determine eligibility. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research. Hence, the recruitment of participants conforms to the principle of distributive justice.

10.2 Informed Consent

Federal regulations 45 CFR 46.111(a)(5) require us to seek informed consent from each patient. Study personnel obtaining informed consent are responsible for ensuring that the patient understands the risks and benefits of participating in the study, answering any questions the patient may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's

willingness to permit the patient's continued participation in the trial. The study personnel obtaining informed consent will make every effort to minimize coercion. We will inform all patients of the objectives of the study and the potential risks. We will use the informed consent document to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to confirm that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures including administration of study agent.

For additional details, see Section 3.6.

10.3 Withdrawal of Consent

Participating patients may withdraw or be withdrawn (by the treating physician or investigator) from the trial at any time without prejudice. Site personnel will include data up to the point of withdrawal in the trial analysis, unless consent to use data is also withdrawn. Site personnel will record consent prior to receipt of study drug, which will constitute a screen-failure. Withdrawal of consent after randomization and administration of one or more doses of study drug will lead to discontinuation of study interventions but site staff will request access to medical records for data related to the trial.

10.4 Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data. At no time during the course of this study, its analysis, or its publication will we reveal patient identities in any manner. We will collect the minimum necessary data containing patient or provider identities. All patients will be assigned a unique study ID number for tracking. We will enter all data collected for this study into a secure online database. We will maintain all data in the secure online database until the time of study publication. At the time of publication, we will generate a de-identified version of the database. Further, we will use tools within the secure online database so that only the coordinating center and investigators from the enrolling site will have access to data from participants enrolled at that site.

11. ADVERSE EVENTS

Assuring patient safety is an essential component of this protocol. Lopinavir/ritonavir is approved by the Food and Drug Administration and there is an have been used in clinical practice for decades with a well-established safety profile. Use of lopinavir/ritonavir for the treatment of acute respiratory infection due to COVID-19, however, raises unique safety considerations. This protocol addresses these considerations through:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events with receipt of lopinavir/ritonavir
2. On-study monitoring of co-interventions (e.g., newly prescribed medications) and patient characteristics (e.g., healthcare utilization, clinically obtained electrocardiogram) to intervene before adverse events occur.
3. Systematic collection of safety outcomes relevant to use of lopinavir/ritonavir in this setting.

4. Structured reporting of adverse events

11.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.

Serious Adverse Event: A serious adverse event is any adverse event that results in one of the outcomes listed in section 11.3 below.

Adverse Reaction: An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse events where there is a reason to conclude that the study intervention caused the event.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with risks outlined in the study protocol or investigator brochure), serious, and meets the definition of a suspected adverse reaction.

11.2 Safety Monitoring

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. The Investigators will determine daily if any adverse events occur during the period from enrollment through **study day 16** (or 48 hours after completion of the study drug administration) and will determine if such adverse events are reportable. Thereafter, adverse events are not required to be reported to the IRB unless the investigator feels the adverse event was related to study drug or study procedures.

The following adverse events will be considered reportable and thus collected in the adverse event case report forms:

- Serious adverse events
- Non-serious adverse events that are considered by the investigator to be related to study procedures or of uncertain relationship (Appendix C)
- Events leading to permanent discontinuation of study drug.

Study-specific clinical outcomes (Primary, Secondary and Safety Outcomes and Assessments During the Study), including serious outcomes such as organ failures and death, are systematically recorded in the case report forms and are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug or the conduct of study procedures (or of uncertain relationship) as outlined in Appendix C.

After randomization, adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the VCC their assessment of the

potential relatedness of each adverse event to the study drug or protocol procedure via electronic data entry. Investigators will assess if there is a reasonable possibility that the study procedure caused the event, based on the criteria outlined in Appendix C. Investigators will also consider if the event is unexpected. Unexpected adverse events are events not listed in the study protocol and the investigator brochure for Lopinavir/ritonavir. Investigators will also determine if adverse events are unanticipated given the patient's clinical course, previous medical conditions, and concomitant medications.

If a patient's treatment is discontinued as a result of an adverse event, study site personnel must also report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms.

11.3 Serious Adverse Events

Serious adverse event collection begins after randomization and study procedures have been initiated. If a patient experiences a serious adverse event after consent, but prior to randomization or starting study procedures, the event will NOT be collected. Study site personnel must alert the VCC of any **serious and study procedure related** adverse event within 24 hours of awareness of the event regardless of suspected causality. The site Investigator must sign off on the initial report within three (3) days of study team's awareness of the SAE. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix C for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs)

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization

  As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Persistent or significant disability/incapacity

  As per http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm: Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Reportable serious adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events will be collected through **Study Day 16 (or** 48 hours after completion of the study drug administration), regardless of the investigator's opinion of causation.

12. Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of participants in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations with respect to:

- Review of adverse events
- Review of every death occurring on study
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

The DSMB will consist of members with expertise in acute infections, acute lung injury, emergency medicine, biostatistics, ethics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The unblinded statistician will be responsible for the preparation of all DSMB and adverse event reports and may review unblinded data. The DSMB will develop a charter and review the protocol and sample consent form during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter with the assistance of the VCC. When appropriate, conference calls may be held in place of face-to-face meetings. Recommendations to end, modify, or continue the trial will be prepared by the DSMB executive secretary. Recommendations for major changes, such as stopping the trial, will be communicated immediately. Other recommendations will be distributed in writing to the VCC and sIRB, which will distribute with instructions for reporting to local IRBs when appropriate.

We will comply with the principles and approaches espoused by the NIH NHLBI guidance found here:

https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-policy-data-and-safety-monitoring-extramural-clinical-studies

13. APPENDICES

Appendix A. Schedule of Events

Schedule of Events

Description:	Date of Randomization	Days 1-14	Days 15-16	Day 29
Confirmation of SAR-CoV-2 positive test result	X			
Home medications	X			
Verification of Inclusion/Exclusion Criteria	X			
Remote consent	X			
Randomization	X			
IP shipped to subject	X			
Self-Administered Dosing		X		
Self-Reported Symptom Survey		X	X	X
Assessment of Adverse Events		X	X	X
Modified COVID Ordinal Outcome Scale		X	X	X
Ventilator Status		X	X	X
ICU Status		X	X	X
Oxygen Status		X	X	X
Hospital Length of Stay		X	X	X
Vital Status				X
End of Study				X

Appendix B. Potential medication interactions with lopinavir/ritonavir

Medications considered to present a potential interaction with lopinavir/ritonavir, which if ordered during the 14-day study period, will prompt study personnel to discuss with treating clinicians the risk-benefit assessment of this medication and potential need for additional monitoring: flecainide, mefloquine, methotrexate, mexilitine, rifampicin, rifapentine, amiodarone, cimetidine dofetilide, phenobarbital, phenytoin, or sotalol, propafenone, astemizole, terfenadine, alfuzosin, apalutamide, ranolazine, dronedarone, rifampin, lurasidone, cisapride, pimozide, ergot-containing medicines (including dihydroergotamine mesylate, ergotamine tartrate, methylergonovine), lovastatin, simvastatin, lomitapide, sildenafil, triazolam, midazolam, rivaroxaban, fluticasone and anticoagulants or St. John's Wort.

Appendix C: Adverse Event Reporting and Unanticipated Events

As noted in section 11, investigators will report all "serious adverse events," defined as adverse events that are serious and have a reasonable possibility that the event was due to a study drug or procedure (or of uncertain relatedness), to the VCC within 24 hours. The VCC will then notify the single Institutional Review Board (sIRB).

The National/Lead Investigator at the VCC will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study drug or study procedure, as outlined in 21 CFR 312.32**(a)**(1), and below. The CC unblinded statistician will also determine if the event is unexpected for lopinavir/ritonavir. An adverse is considered "unexpected" if it is not listed in the investigator brochure or the study protocol (21 CFR 312.32(a)). If a determination is made that a serious adverse event has a reasonable possibility of having been caused by a study procedure or the study drug, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

To enhance safety monitoring, the VCC will report every death by coded group (and potentially unblinded group upon request) to the DSMB. The VCC will also report all unexpected deaths, serious and treatment related adverse events, and SUSARs to the DSMB, and sIRB within 7 days after receipt of the report from a clinical site. A written report will be sent to the DSMB and the sIRB within 15 calendar days. The DSMB will also review all reported adverse events and clinical outcomes during scheduled interim analyses. The VCC will distribute the written summary of the DSMB's periodic review of reported adverse events to the sIRB. The VCC will provide to AbbVie Pharmacovigilance any safety findings for lopinavir/ritonavir (without disclosing protected health information) during the conduct of the trial per contractual language.

C.1. Unanticipated Problems (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied.
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

C.2. Determining Relationship of Adverse Events to Study Drug or Study Procedures

Investigators will be asked to grade the strength of the relationship of an adverse event to study drug or study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state

or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.

- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
- Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

C.3. Clinical Outcomes that may be Exempt from Adverse Event Reporting

Study-specific outcomes of acute respiratory infection, COVID-19, and critical illness will be systematically collected for all patients in both study group and are exempt from adverse event reporting unless the investigator considers the event to be Definitely or Possibly Related (or of an Uncertain Relationship) to the study drug or study procedures. Examples of study-specific clinical outcomes include:

- Death not related to the study procedures.
- Neurological events
    - Seizure
- Cardiovascular events
    - Receipt of vasopressors
    - Atrial or ventricular arrhythmia
    - Cardiac arrest
- Respiratory events
    - Hypoxemia requiring supplemental oxygen
    - Acute respiratory distress syndrome
    - Receipt of mechanical ventilation
    - Receipt of extra-corporeal membrane oxygenation
- Gastrointestinal events
    - Elevation of aspartate aminotransferase or alanine aminotransferase
    - Acute pancreatitis
- Renal events
    - Acute kidney injury
    - Receipt of renal replacement therapy
- Endocrine events
    - Symptomatic hypoglycemia
- Hematologic or coagulation events
    - Neutropenia, lymphopenia, anemia, or thrombocytopenia
- Dermatologic events
    - Severe dermatologic reaction (e.g., Steven's Johnson Syndrome)

Note: A study-specific clinical outcome may also qualify as a reportable adverse event. For example, a ventricular arrhythmia that the investigator considers Definitely or Possibly Related to the study drug would be both recorded as a study-specific clinical outcome and reported as a Serious and Definitely or Possibly Related Adverse Event.

C.4. Decision tree for determining if an adverse event is reportable

Figure 1. Decision tree for determining if an adverse event is reportable

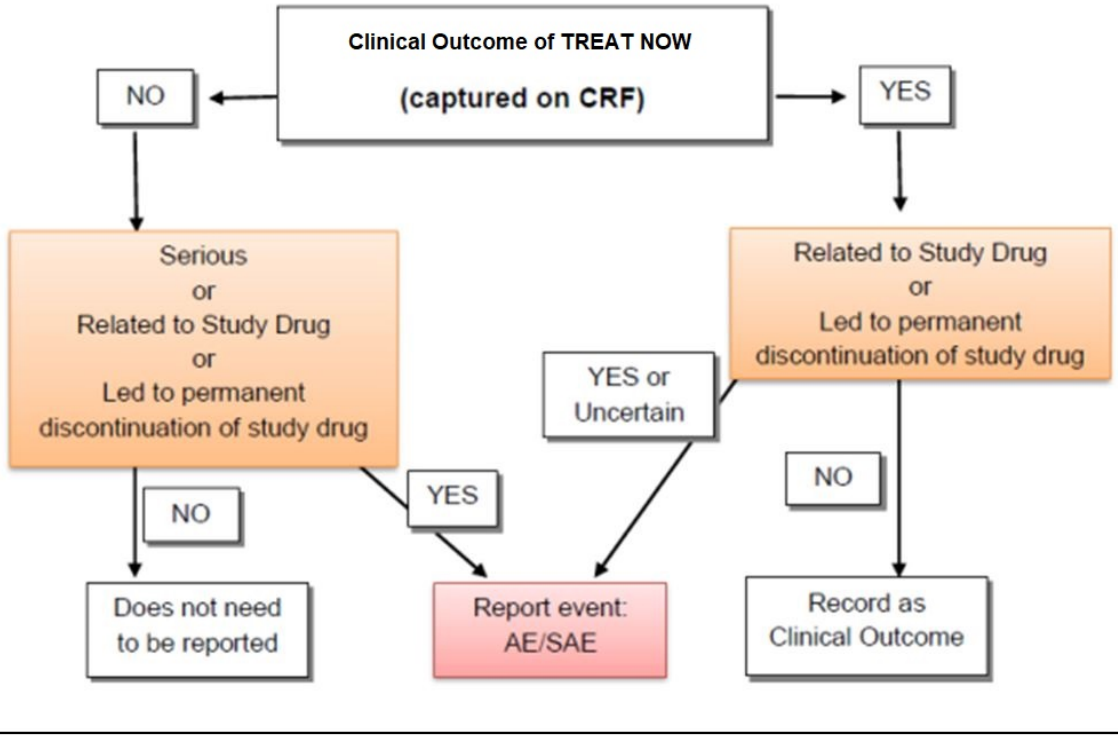

Figure adapted from Ranieri VM, Thompson BT, Barie PS et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366 (22):2055-64. PMID: 22616830.

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Statistical Analysis Plan

We would like to acknowledge the Cambridge University Hospitals Clinical Trials Unit for the development of the template (version CCTU/TPLV2), which was modified by the Michigan Institute for Clinical & Health Research (MICHR).

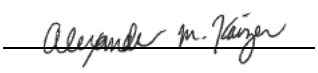
TRIAL FULL TITLE	Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) for COVID-19
SAP VERSION	1.1
SAP VERSION DATE	12/23/2021
TRIAL STATISTICIAN	Alexander Kaizer, PhD
Protocol Version (SAP associated with)	1.6
TRIAL PRINCIPAL INVESTIGATORS	Adit A. Ginde, MD, MPH Nathan I. Shapiro, MD, MPH
SAP AUTHOR	Alexander Kaizer

1 SAP Signatures

I give my approval for the attached SAP for TREAT NOW dated 12/23/2021:

Statistician (Author)

Name: Alexander M. Kaizer, PhD

Signature: 

Date: 12/24/2021

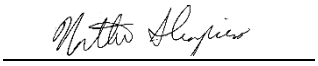
Principal Investigators

Name: Adit A. Ginde, MD, MPH

Signature: 

Date: 12/24/2021

Name: Nathan I. Shapiro, MD, MPH

Signature: 

Date: 12/24/2021

2 Table of Contents

3 Abbreviations and Definitions

ACE-I	Angiotensin-converting-enzyme inhibitor
ARB	Angiotensin II receptor blocker
ADR	Adverse drug reaction
ACE	Angiotensin-converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
AR	Adaptive randomization
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BID	"Bis in die" (twice daily)
CC	Coordinating Center
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CYP3A	Cytochrome P4503A
DCC	Data Coordinating Center
DSMB	Data and safety monitoring board
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EKG	Electrocardiogram
FDA	Food & Drug Administration
GFR	Glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration
ICU	Intensive care unit
ID	Identification
IL1	Interleukin-1
IL6	Interleukin-6
IP	Investigational product
IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
IV	Intravenous
IVY Network	Influenza Vaccine Effectiveness in the Critically Ill Network
KDIGO	Kidney Disease Improving Global Outcomes
LFT	Liver function test

LPV/r	Lopinavir/ritonavir
MERS-CoV	Middle East respiratory syndrome coronavirus 2
MIC	Minimum inhibitory concentration
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NSAIDs	Nonsteroidal anti-inflammatory drug
pH	Potential for hydrogen
PI	Principal investigator (a clinician responsible for one site)
PK/PD	Pharmacokinetics/pharmacodynamics
PPE	Personal protective equipment
PPoS	Predictive probability of success
QD	“quaque die” (once daily)
QID	“quater in die” (four times daily)
QR code	Quick response code
QTc	QT interval corrected for heart rate
RCT	Randomized control trial
REDCap	Research Electronic Data Capture
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S/F	SpO_2/FiO_2 ratio
sIRB	Single IRB
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected unexpected serious adverse reaction
US	United States
VAS	Visual Analog Scale

4 Introduction

4.1 Preface

Effective therapies for COVID-19 are urgently needed. Lopinavir/ritonavir (Kaletra), an antimicrobial agent used to treat HIV-1, has demonstrated in vitro inhibition of SARS-CoV-2, the virus that causes COVID-19. Initial clinical data have suggested possible relevance as a therapeutic agent when administered early in the disease course of patients with COVID-19. The TREAT NOW study was designed to test the hypothesis that lopinavir/ritonavir reduces disease progression and improves clinical status measured using a seven point at day 15 following receipt of study drug when compared with placebo. The TREAT NOW study is a multicenter, blinded, non-matching placebo-controlled, randomized clinical trial to evaluate the superiority of active therapy (lopinavir/ritonavir) versus placebo control. Briefly, patients testing positive for SARS-CoV-2 infection in an outpatient setting are contacted by research coordinators and invited to participate. Adults with a positive SARS-CoV-2 test are either self-referred or identified via review of testing records at participating sites. Patients who are still symptomatic and who are within six days of symptom onset are invited to participate. Eligible participants who provide their consent to participate using an electronic system undergo comprehensive baseline data collection via phone survey, the participant is randomized, and study drug or placebo is shipped overnight to the participant's home. The participant then completes a daily web-based medication adherence, symptom burden, and hospitalization survey for sixteen days. Missed surveys result in telephone follow up to complete missing data and to re-engage the participant in completing the study. At day 15, the primary outcome is assessed. Patients are followed up once more at 29 days

4.2 Scope of this statistical analysis plan

The TREAT NOW clinical protocol was developed to adapt to allow for addition of new agents and changing standards of care. In the absence of any planned adaptations, this document is restricted to the statistical design and analysis of a comparison between two groups of participants: patients randomized to receive lopinavir/ritonavir and patients randomized to receive a placebo. If new agents are introduced for testing, or other adaptations are sought, this document will be revised accordingly.

Section 5 introduces and defines the study objectives and endpoints. Study methods including the overall design, inclusion/exclusion criteria, randomization, and blinding are in Section 6. Sample size justifications are in Section 7. Section 8 discusses the analysis populations and planned interim analyses. Subject disposition, derived variable definitions, and protocol deviations are defined in Section 9. Sections 10 and 11 detail the planned efficacy and safety analyses, respectively. The final sections, after Section 12, note reporting conventions, any updates to the SAP and/or protocol after SAP approval, and references.

5 Study Objectives and Endpoints

5.1 Study Objectives

To determine whether early treatment with lopinavir/ritonavir improves clinical status at 15 days when compared to placebo in outpatient adults with COVID-19. Secondary objectives include describing the safety profile of lopinavir/ritonavir, and to determine whether the clinical progression is improved through to Day 29.

5.2 Treatment arms

The active treatment arm of lopinavir/ritonavir (LPV/r) consists of standard dosing with 400mg/100mg taken orally twice daily for 28 doses. Medication dose packs contain all 28 doses labelled by study day. The LPV/r dosing is based upon extensive PK/PD study evaluations in healthy and HIV+ subjects.

The control arm consists of unmatched placebo taken orally twice daily for a total of 28 doses. Medication dose packs will contain all 28 doses labelled by study day. Given the unmatched placebo pill to LPV/r, exclusion will be exercised to ensure two individuals from the same household are not enrolled in the study and that telephone assessments during the study avoid discussion of the appearance of the study medication.

5.3 Endpoints/Outcomes

In this section endpoints/outcomes are described with how they should be operationalized for analysis. Additional information on the study population(s) are defined in Section 8.2 with respect to those included for analysis. Per the protocol, timing of study procedures is based on the time of randomization, which is defined as Baseline. Study Day 1 is defined as the day of receipt of the first dose of the study drug.

Primary outcome:

The primary outcome is the daily status based on the proposed Modified COVID Ordinal Outcomes Scale from Study Day 1 through Study Day 15:

1. Death
2. Hospitalized on mechanical ventilation or ECMO
3. Hospitalized on supplemental oxygen
4. Hospitalized not on supplemental oxygen
5. Not hospitalized with symptoms and limitation in activity
6. Not hospitalized with symptoms but with no limitation in activity
7. Not hospitalized without symptoms nor limitation in activity

Each daily status is derived primarily from the daily study survey through day 16 after randomization and the chart review on day 29 after randomization. This is a longitudinal measure of the ordinal outcome from receipt of study medication (Study Day 1) to completion of study treatment (Study Day 15).

Secondary outcomes:

The secondary outcomes are described below with details on operationalization:

- Modified COVID Ordinal Outcome Scale on Study Day 8
    - The ordinal outcome of the previously defined scale on Study Day 8 after one week of treatment.
- Modified COVID Ordinal Outcome Scale on Study Day 15
- Modified COVID Ordinal Outcome Scale on Study Day 29
    - The ordinal outcome of the previously defined scale on Study Day 29 after one month of treatment receipt.
- Proportion of patients hospitalized through Study Day 29
    - A dichotomous indicator if the participant was hospitalized at any point through Study Day 29 as reported on daily surveys or through the Day 29 Chart Review.
- Time to hospitalization through Study Day 29
    - The number of days from receipt of study medication (Study Day 1) to first

hospitalization for any reason through Study Day 29.

- Time to symptom resolution through Study Day 29
    - The number of days from receipt of study medication (Study Day 1) to resolution of all symptoms reported without recurrence. For example, if a participant reports no symptoms on the daily survey on Study Day 5, but then symptoms are reported again on Study Days 6 through 8 with resolution of all symptoms on Study Day 9, the number of days for resolution would be 9 and not 5 to reflect the recurrence of symptoms.
- All-cause, all-location mortality up to Study Day 29
    - A binary variable indicating death for any reason from receipt of study drug (Study Day 1) through Study Day 29.
- Oxygen-free days through Study Day 29
    - The number of days derived from the Modified COVID Ordinal Outcome Scale where there is no reported supplemental oxygen, mechanical ventilation, or ECMO from receipt of study drug (Study Day 1) to Study Day 29 during hospitalization. Death before Study Day 29 will be penalized by using a value of -1 free days.
- Fever-free days through Study Day 29
    - The number of days where fever is reported as “None” versus “Mild”, “Moderate”, or “Severe” based upon daily surveys between receipt of study drug (Study Day 1) and Study Day 29. Death before Study Day 29 will be penalized by using a value of -1 free days.
- Ventilator-free days through Study Day 29
    - The number of days derived from the Modified COVID Ordinal Outcome Scale where there is no reported mechanical ventilation or ECMO from receipt of study drug (Study Day 1) to Study Day 29. Death before Study Day 29 will be penalized by using a value of -1 free days.
- Vasopressor-free days through Study Day 29
    - The number of days from receipt of study drug (Study Day 1) to Study Day 29 based upon the Study Day 29 Chart Review where no vasopressor use is denoted. Death before Study Day 29 will be penalized by using a value of -1 free days.
- ICU-free days through Study Day 29
    - The number of days from receipt of study drug (Study Day 1) to Study Day 29 based upon the Study Day 29 Chart Review where there is no portion of the day spent in the ICU. Death before Study Day 29 will be penalized by using a value of -1 free days.
- Hospital-free days through Study Day 29
    - The number of days from receipt of study drug (Study Day 1) to Study Day 29 based upon daily surveys and the Study Day 29 Chart Review where there is no portion of the day spent admitted to a hospital setting. Death before Study Day 29 will be penalized by using a value of -1 free days.

Safety outcomes:

Safety outcomes to be included in the safety analysis for this trial include all potentially associated adverse events (PAAEs) as well as other events of interest including, but not necessarily limited to:

- Seizure
- Atrial or ventricular arrhythmia
- Cardiac arrest
- Receipt of renal replacement therapy

- Severe dermatologic reaction
- *Elevation in aspartate aminotransferase or alanine aminotransferase to twice the local upper limit of normal AND at least doubling over known baseline
- *Acute pancreatitis
- *Acute kidney injury by KDIGO criteria
- *Symptomatic hypoglycemia
- *Anemia or thrombocytopenia

* For participants whose symptoms are significant enough to trigger a clinical work-up and thus have clinically available testing

6 Study Methods

6.1 Overview of study Design

The study is a multicenter, blinded, non-matching placebo-controlled, randomized clinical trial to evaluate the superiority of active therapy (lopinavir/ritonavir) versus placebo control. Patients, treating clinicians, and study personnel are blinded to study group assignment. Randomization uses permuted blocks and is stratified by site and age (≥65 years or <65 years) in a 1:1 ratio through a central electronic system. The primary outcome, measured from Study Day 1 (receipt of study drug) to Study Day 15, is a seven-level ordinal scale describing the patient's clinical status defined in Section 5. The planned analysis is a longitudinal Bayesian proportional odds model with a skeptical prior, and is powered to detect an odds ratio of greater than 1.75.

6.2 Inclusion-Exclusion Criteria and General Study Population

Patients aged ≥18 years who have laboratory-confirmed SARS-CoV-2 infection by RT-PCR or other molecular test within the past 6 days, whose symptoms began ≤6 days previously, and who currently remain with at least one symptom are eligible to participate. Qualifying symptoms are cough, fever, shortness of breath, chest pain, abdominal pain, nausea/vomiting, diarrhea, body aches, weakness/fatigue.

Detailed exclusion criteria are listed in the protocol. They include known contraindications for lopinavir/ritonavir, clinical conditions increasing the risk of adverse events associated with lopinavir/ritonavir, known pregnancy or breast feeding, known to be a prisoner, inability to comply with study procedures, and inability to provide informed consent or complete daily symptom surveys in English or Spanish during the two-week observational period.

6.3 Randomization and Blinding

Eligible patients will be randomized in a 1:1 ratio to the intervention arm (lopinavir/ritonavir) or the control arm (placebo). Randomization is stratified by site and age (≥65 years versus <65 years) and uses permuted small block randomization. Patients, treating clinicians, trial personnel, and outcome assessors are blinded to group assignment. Only the investigational pharmacy (who is distributing study medication), the Data Coordinating Center (who is managing the randomization systems including generating the randomization sequence), and one member of the statistical team (who is preparing closed DSMB interim reports) are unblinded.

To maintain the blind, study medication is dispensed with packaging and labelling that does not indicate whether the drug is a placebo or active treatment. Unblinding will occur only if required for subject safety or treatment at the request of the treating clinician and will be done by the

Investigational Pharmacy.

6.4 Timing of study procedures and outcomes assessments

The day of randomization is defined as Baseline and the receipt of the study drug is defined as "Study Day 1". It is possible for it to take up to two days for study medications to arrive at a participant's home. For the purposes of analysis, Study Day 1 will be counted as the day on which study medications are received by the participant. To ensure symptoms are assessed daily while on study, and to ensure the primary outcome can be measured through Study Day 15, symptoms are collected daily from the day following randomization to sixteen days following randomization. The symptoms assessed on Study Day 1 (day of receipt of medication) to Study Day 15 are included in the measurements for this trial. At Study Day 15, the primary outcome is assessed. At Study Day 29, additional outcomes are assessed.

7 Sample Size

This study is designed to be analyzed using a Bayesian approach, accepting the possibility of adaptations or sample size adjustments as the trial progresses. Although the design as detailed is Bayesian in nature, a frequentist sample size and target power are provided for consistency with FDA guidance and recommendations. To provide a sample size estimate, we calculated a sample size of 540 patients equally distributed among study arms is needed to have 90% power to detect an odds ratio of 1.75 or greater assuming a traditional proportional odds model and a type I error of 0.05, as proposed by Whitehead (1993). Accounting for an approximate 10% loss to follow-up rate, we plan to enroll 600 patients

An example of the difference between study arms resulting in such an odds ratio is shown in the table. This is based on recommendations from the World Health Organization for COVID-19 Master Protocols that were in place at the time this study was designed

Category	Placebo Arm Proportion	Treatment Arm Proportion
1-Death	1%	0.6%
2-Hospitalized on mechanical ventilation or ECMO	3%	1.8%
3-Hospitalized on supplemental oxygen	4%	2.4%
4-Hospitalized not on supplemental oxygen	3%	1.9%
5-Not hospitalized with symptoms and limitation in activity	10%	6.6%
6-Not hospitalized with symptoms but with no limitation in activity	24%	18.7%
7-Not hospitalized without symptoms nor limitation in activity	55%	68.1%

8 General Analysis Considerations

Here, we describe overarching guidelines that will be followed in the statistical analysis of the TREAT NOW study. The timing and scope of each analysis, the analysis datasets, the approach to handling

missing data, covariate adjustment, subgroup analysis and stopping guidelines are provided. In subsequent sections, the approach to describing the data and modeling the outcomes of interest are described.

8.1 Timing of Analyses

The final analysis will be performed after all subjects enrolled have completed their Day 29 data collection or dropped out prior to their Day 29 data collection, and data are declared query free. Interim analyses are detailed below for safety, efficacy, and futility and will be performed for the primary outcome based on a database pull for interim analyses. At conclusion of the trial and after resolution of all queries, the database will be locked.

8.2 Analysis Populations

The analysis populations are defined below. A participant's inclusion or exclusion status with regard to each analysis population will be set prior to breaking the blind for final analyses based on the criteria as outlined.

8.2.1 Intention to Treat Population

- All subjects who have receipt of study drug (Study Day 1) based upon their randomized allocation.
- Given the study design whereby patients are shipped study drug from a central pharmacy, there might be times when the drug does not get delivered to the patient. In these rare instances the patient will be excluded. All other subjects will be included, and they will be analyzed according to which group the patient was assigned. Thus, the intent to treat (ITT) analysis set includes all subjects who were randomized and received the study drug at their provided address.

8.2.2 Per Protocol Population

- All subjects who receive study drug, report taking at least one dose, and who complete their Study Day 15 survey will be included in the per protocol population.
- Patients will be classified according to the treatment they received with confirmation of receipt from the study pharmacy.

8.2.3 Safety Population

- All subjects who received any study treatment (including control) and reported taking at least one dose but excluding subjects who drop out prior to receipt of the study drug. In the unlikely case a participant receives the incorrect study drug, patients will be grouped according to the treatments that they received in any safety analyses. If a participant receives both placebo and active treatment, they will be considered as receiving active treatment.

8.3 Covariate adjustment

The main analysis of the primary outcome will be a covariate adjusted proportional odds model. Covariates that will be adjusted for include

- Race/ethnicity defined as a single categorical variable for non-Hispanic White/Caucasian, non-Hispanic Black/African American, Hispanic, Other.
- Age as a continuous variable in years; modeling will assess for linear effect or cubic splines based on the study data.
- Gender as a categorical variable for male, female, undifferentiated, and no answer
- Duration of acute respiratory infection symptoms prior to study drug receipt in days calculated as the duration reported at enrollment for randomization plus the additional days

until receipt of study drug

- Presence of comorbidities as a dichotomous variable for presence of any or absence of all of the following: hypertension, diabetes mellitus, obesity, chronic kidney disease, chronic cardiopulmonary conditions, or immunosuppressive conditions.
- Monoclonal antibodies taken for the treatment of COVID-19 prior to randomization defined as a binary variable (yes/no)
- SARS-CoV-2 vaccinations were added to the data collection on May 14th, 2021. After that time, enrolled subjects will be categorized as fully vaccinated (at least 14 days after 2nd dose of SARS-CoV-2 mRNA vaccine or after single dose of J&J vaccine prior to randomization); partially vaccinated (receipt of one or more doses of SARS-CoV-2 vaccine but not fully vaccinated prior to randomization); and not vaccinated. Between December 14th, 2020 (first day of public vaccination in the US under EUA) and May 13th, 2021, vaccination status will be recorded as missing. Prior to December 14th, 2020, vaccination status will be recorded as not vaccinated.
- Time period when date of randomization occurred defined as a categorical variable in quarters (3 month) periods beginning with June 2020-August 2020, September 2020-November 2020, December 2020-February 2021, etc.

Center effects will be accounted for with the specification of a random intercept. The defined groupings above may be modified to collapse groups pending the available data at time of final study analysis.

8.4 Missing Data

Missing outcome data for an analysis population will be imputed when necessary using multiple imputation. Outcomes using the Bayesian longitudinal proportional odds model, which includes the primary outcome, will not use imputation since the model facilitates smoothing over missing responses (i.e., the model can still be used even if a participant has missing day(s) of response data). Data on age, gender, race/ethnicity, comorbidities, and duration of acute respiratory infection prior to randomization should not be missing as they are collected as part of enrollment, however imputation procedures will be used in cases of missing values.

8.5 Interim Analyses and Data Monitoring

8.5.1 Purpose of Interim Analyses

Interim analyses are planned for safety, efficacy, and futility. The results of the interim analyses will be reported to the DSMB, along with the stopping guidelines described in this Statistical Analysis Plan. The DSMB may request additional interim analyses. Such requests will be fulfilled by the unblinded statistician and will not be reported outside of the DSMB meeting.

8.5.2 Planned Schedule of Interim Analyses

The first interim analysis is planned after at least the first 50 participants have been enrolled and achieved follow-up through at least Study Day 15. This first analysis will present only safety data to the DSMB. The second and subsequent interim analyses will include both safety and efficacy data, and are planned to occur after at least 200 participants have been enrolled and have their primary outcome observed at Study Day 15. Futility interim analyses will begin after approximately 400 participants have been observed and will be conducted in addition to interim analyses for safety and efficacy.

This trial is planned to be analyzed using a Bayesian approach, and so a strict interim analysis schedule is not prespecified. Instead, the schedule for subsequent interim analyses will be decided by the DSMB based upon the rate of accrual, the safety and feasibility data from at least the first 200

participants, opportunities to add new agents, and other relevant considerations.

8.5.3 Adaptations

The statistical design of this study is sufficiently flexible to allow for future adaptations. However, no adaptations are currently planned. Should new agents become available for inclusion in the study, or should there be sufficient evidence to warrant changes in the planned randomization allocation probabilities or sample size, the adaptations will be encoded in a revision to this document before being implemented.

8.5.4 Stopping Rules

Given the Bayesian nature of the analysis, the *posterior probability* of the odds ratio for the primary outcome exceeding certain thresholds will be used to guide decisions to stop the trial early for efficacy or harm. These are:

Probability	Evidence For	Action Trigger
$P_1 = P(OR > 1 \mid data)$	Any benefit	$P_1 > 0.95$
$P_2 = P(OR < 1 \mid data)$	Inefficacy or potential harm	$P_2 > 0.90$

The criteria for P_1 represents scenarios where an intervention arm would stop early for efficacy, whereas P_2 represents early termination of an intervention arm for inefficacy or potential harm.

Interim monitoring for futility will be based on the *posterior predictive probability* that P(concluding efficacy at N=300 per group|interim data). For the calculation of PPoS, the efficacy threshold on study completion will be based on the posterior probability that P(OR > 1 | data) > 0.90. The posterior predictive probability of success (PPoS) will be estimated via upstrapping the remaining number of participants to be enrolled from participants who have completed through Study Day 15 regardless of level of missing data (Crainiceanu and Crainiceanu 2020). The PPoS will be based on 1,000 upstraps of the "completed" trial with stopping rules based on the following table:

Predictive Probability of Success (PPoS) Action Trigger	Action
PPoS < 0.10	Stop for futility
$0.10 \leq$ PPoS < 0.25	Consider stopping for futility based on trial characteristics (e.g., accrual), secondary endpoints, and external factors
PPoS $\geq$ 0.25	Continue trial

8.5.5 Considerations for Multiplicity of Testing

Unlike a frequentist design with confidence intervals and p-values relating to the unknown parameters, a Bayesian design conditions on the data to estimate the unknown parameters. Therefore, the type of control for multiplicity used in a frequentist approach is inappropriate. However, it is not uncommon to attempt to understand the frequentist operating characteristics for Bayesian designs. We note that a 5% type I error rate with identical assumptions to detect an OR=1.75 achieves 86.4% power with a target sample size of 600. With regards to repeated evaluations of efficacy using the Bayesian approach, the posterior probability is an estimate of the unknown parameter conditional on the data collected thus far and any prior estimates of the posterior probability are irrelevant, and so multiplicity adjustments are not warranted and would be inappropriate.

9 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, minimum, 1st quartile, 3rd quartile, and maximum. All categorical variables will be reported as the frequency and percentages of observed levels with a clear definition of the denominator. In general, summary tables will be based on the relevant population (e.g., ITT, safety) and structured with a column for each study arm and will be annotated with the total sample size relevant to that table/treatment, including the number of missing observations.

9.1 Descriptive analysis

Using data pooled across all sites, the study sample will be characterized based on demographic and clinical variables measured at randomization, unless otherwise indicated. Specifically, the following variables will be described:

1. Age (years)
2. Sex (male, female, undifferentiated, no response)
3. Race (Black/African American, White/Caucasian, American Indian/Alaskan Native, Asian, Native Hawaiian/Other Pacific Islander, other, no answer)
4. Ethnicity (Hispanic, non-Hispanic)
5. Race/ethnicity (non-Hispanic Black/African American, non-Hispanic White/Caucasian, Hispanic, other)
6. Body mass index (kg/m^2)
7. Presence of comorbidities (yes/no):
    a. chronic cardiac disease
    b. chronic pulmonary disease
    c. chronic kidney disease
    d. chronic liver disease
    e. chronic neurological disease
    f. malignant neoplasm
    g. chronic hematologic disease
    h. AIDS/HIV
    i. obesity
    j. diabetes with complications
    k. diabetes without complications
    l. rheumatologic disorder
    m. malnutrition
    n. immunosuppressive conditions
8. Tobacco product use (current, former, never)
9. E-cigarette or vaping product use (current, former, never)
10. Chronic use of medication (yes/no):
    a. ACE inhibitors
    b. angiotensin receptor blockers
11. Receipt of azithromycin in the past week
12. Presence of symptoms (yes/no):
    a. Cough
    b. Fever
    c. Shortness of breath
    d. Chest pain
    e. Abdominal pain

f. Nausea
g. Diarrhea
h. Body aches
i. Weakness/fatigue

13. Total number of symptoms reported (count)
14. Symptom duration (days)

9.2 Subject disposition

The number of participants completing each stage of the trial will be summarized with frequencies and percentages to describe the number screened, the number randomized, the number reaching target data collection times by arm at Study Day 8, Study Day 15 (primary), and Study Day 29 for collection of the primary ordinal outcome status, and the number that dropped out by arm and the accompanying reason where known (e.g., death, toxicity, withdrew consent). A CONSORT diagram will be generated (Schulz et al. 2010).

9.3 Derived variables

This study involves several derived variables, such as body mass index and the seven-level ordinal outcome scale. During the data collection process, each component of the derived variable is collected and the first stage in data analysis will be to generate and validate the derived variable. Depending on the distribution of the seven-category modified COVID-19 ordinal outcomes scale, certain categories may need to be combined based upon few or no events.

The primary outcome through Study Day 15 will be derived primarily through the daily surveys (from Days 1 to 16 post-randomization) and supplemented by the Study Day 29 Chart Review to verify details about hospitalization or other healthcare encounters recorded. The method for derivation of other variables not described will be clearly articulated in the analysis report if needed.

9.4 Treatment compliance, protocol deviations and protocol violations

Major protocol deviations and violations will be described. Adherence to the schedule for taking study medications will be reported. Major protocol deviations that will be reported are failure of participant to adhere to the study medication schedule, errors in shipping and handling of study medication including shipping the incorrect medication, and other protocol deviations deemed by the study executive committee to affect the overall integrity of the data. Any such determination will be made before unblinding to treatment arm.

10 Efficacy Analyses

All continuous and categorical variables will be summarized as described previously. The analytic approach is Bayesian with results presented as credible intervals and posterior probabilities for specific hypotheses as defined in the following sections unless otherwise noted.

10.1 Primary Efficacy Analysis

The primary outcome of the Modified COVID Ordinal Outcomes Scale from Study Day 1 through Study Day 15 will be evaluated in the ITT dataset using a Bayesian longitudinal proportional odds model. The model will include a random intercept for each participant to account for the repeated measurements over time to calculate the posterior probability that a treatment arm compared to the placebo-controlled arm has an OR > 1, suggesting any benefit for the treatment. The proportional odds assumption will be examined using graphical methods—e. g., the logit of the empirical cumulative distribution function of the ordinal scale should be parallel among categories of

covariates. If proportionality is clearly violated, we will consider partial proportional odds or non-proportional odds models.

The model will be adjusted for the variables described in Section 8.3. To account for changes in the effect size between treatment groups from Study Day 1 to Study Day 15, an interaction between randomized group and time will be included. Time will initially be modeled using a cubic spline, but it may be modified to a simpler or more complex representation of time if needed to appropriately model the effect over time.

The prior for the intercept for the proportional odds regression model will assume a Dirichlet distribution. The treatment effect, as defined as a log odds ratio in the model, will have a normal prior defined so that $P(OR > 1) = P(OR < 1) = 0.5$ (i.e., equally as harmful as beneficial) and $P(OR > 2) = P\left(OR < \frac{1}{2}\right) = 0.025$ (i.e., large effects in either direction unlikely), with the variance computed to satisfy these criteria. For all other covariates the prior distributions will be normal with mean 0 and a larger variance to reflect the uncertainty of their potential effect.

The convergence of the Markov chain Monte Carlo simulations will be checked via diagnostics, with alternative priors, models, and chain lengths/burn-ins explored if necessary to achieve convergence and satisfy any model assumptions.

10.1.1 Secondary Analyses of Primary Efficacy Endpoint

We will replicate the primary analyses using the per protocol dataset and the safety dataset.

10.2 Secondary Efficacy Analyses

10.2.1 Analyses of Secondary Endpoints

For time-to-event outcomes we will utilize survival models (e.g., Cox proportional hazards models), and dichotomized outcomes will be evaluated using logistic regression. The continuous outcomes such as hospital free days are penalized for death and so an ordinal model will be fit in preference to using linear regression. Secondary endpoint models will be fit using normal priors with mean 0 and larger variance to reflect the uncertainty of their potential effect on all regression coefficients, with convergence evaluated similarly to the primary endpoint.

10.3 Subgroup analyses

The currently recommended approach to subgroup analysis is to prespecify subgroups where there is a clear biological rationale, and otherwise not to create subgroups unless the data indicate differential treatment effects based on potential subgrouping variables. Given how little is known about COVID-19 and possible treatment response, we will examine the potential of differential treatment effects in key subgroups of interest based upon previous definitions unless otherwise noted:

- Age
- Sex
- Race/ethnicity
- BMI
- Baseline renal function defined as known severe chronic kidney disease requiring dialysis, kidney disease not requiring dialysis, no known history of kidney disease
- Hypertension
- Diabetes defined as diabetes with complications, diabetes without complications, not diabetic

- Cardiovascular disease
- Duration of respiratory symptoms prior to randomization

Interactions will not be tested together within the same model but will be tested one by one. Potentially significant subgroups will be identified by evaluating the posterior weight assigned to a model with and without the interaction by Bayesian stacking. If the model including the interaction has a posterior weight of 80% or greater, we will proceed with fitting the model within subgroups. For continuous variables, graphical methods will be used to show how the treatment effect changes over the range of the continuous variable.

11 Safety Analyses

The safety analysis set will be used for safety analyses. Summary statistics will be calculated as described in Section 9. When calculating the incidence of adverse events, or any sub-classification thereof by treatment, time period, severity, etc., each subject will only be counted once for a given safety outcome and any repetitions will be reported separately; the denominator will be the total safety population size.

Three tables summarizing adverse events will be created:

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with number and frequency of such events in each arm/group of the clinical study.

- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of such events in each arm/group of the clinical study.

- Other (Not Including Serious) Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed a frequency threshold of 5% within any arm of the clinical study, grouped by organ system, with number and frequency of such events in each arm/group of the clinical study.

11.1 Adverse Events, Serious Adverse Events, and other Events

The summary statistics will be produced in accordance with section 9. Adverse events, serious adverse events, and other events are defined in Appendix C of the study protocol. The discontinuation of study medication due to potential adverse events or side effects will be summarized by self-reported termination of study treatment and reported adverse events or side effects.

12 Reporting Conventions

For the purposes of the statistical analysis plan report, posterior probabilities and p-values ≥0.001 will be reported to 3 decimal places; values less than 0.001 will be reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 decimal places.

13 References

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